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Deteriorating glucose tolerance status is associated with left ventricular dysfunction - the Hoorn Study

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ABSTRACT

Background: Type 2 diabetes (DM2) is associated with a greater risk of heart failure. The mechanisms underlying this association remain controversial and include diabetes-associated hypertension and obesity, impaired small and large artery function, and a distinct metabolic cardiomyopathy related to hyperglycaemia/hyperinsulinaemia. The proximate causes of heart failure are left ventricular (LV) systolic dysfunction (SDF) and diastolic dysfunction (DDF). We investigated, in a population-based cohort (n=746), the association between glucose tolerance status and SDF and DDF.

Methods and results: The study population consisted of 274 individuals with normal glucose metabolism (NGM), 174 with impaired glucose metabolism (IGM) and 298 with DM2 (mean age 68.5 years). All participants underwent an LV echocardiogram. SDF was defined as ejection fraction <55%. DDF was determined by a sum score of peak A velocity (abnormal, ≥97 cm/s), the difference between A_{pv} and A_{mv} duration (≥41 ms), and left atrial volume (≥57 ml), where cut-off values were based upon the 90th percentile in NGM. In addition, we analysed the ratio of early to late diastolic filling (E/A ratio) on a continuous scale using linear regression analyses. The age- and sex-standardised prevalences in NGM, IGM and DM2 were 13, 14 and 30% for SDF, and 26, 36 and 47% for DDF ($P_{(trend)}$ for both <0.001). After adjustment for sex, age, hypertension, body mass index, prior cardiovascular disease and (micro) albuminuria, DM2 was significantly associated with both SDF (odds ratio (95% CI) 2.04 (1.24 to 3.36)) and DDF (2.42 (1.63 to 3.60)) (90th percentile definition). This was also true for the analyses with the E/A ratio on a continuous scale (regression coefficient β (95% CI) -0.05 (-0.09 to -0.01). After adjustment for sex, age, hypertension, body mass index, prior cardiovascular disease and (micro) albuminuria IGM was not significantly associated with SDF (odds ratio (95% CI) 1.04 (0.58 to 1.88)) or DDF (1.33 (0.86 to 2.06)) using the definition based upon the 90th percentile. However, IGM was significantly associated with DDF if the E/A ratio was analysed on a continuous scale (regression coefficient β (95% CI) -0.05 (-0.10 to -0.01). Additional adjustment for brachial artery flow-mediated vasodilation or arterial stiffness, as measures of large artery function, did not materially alter the results. Hyperglycaemia and hyperinsulinaemia together explained ~30% of the association of DM2 with SDF and ~40% of that with DDF.

Conclusion: DM2 is independently associated with a 2.0-fold greater risk of SDF and a 2.4-fold greater risk of DDF. IGM was not associated with SDF, and the association with DDF was limited to the E/A ratio. These observations may therefore explain the increased risk of systolic and diastolic heart failure in elderly individuals with DM2.

KEYWORDS

Cardiovascular disease, diabetes, echocardiography

INTRODUCTION

Type 2 diabetes (DM2) is associated with an increased risk of heart failure.[1-4] The mechanisms underlying this association remain controversial, and there may be at least three possibilities. First, DM2 is often associated with hypertension and obesity, and these risk factors may in part account for the association of DM2 with heart failure.[5-7] Second, DM2 may lead to heart failure by impairing large and small artery function, because DM2 causes atherothrombotic coronary artery disease,[8] diabetic microangiopathy,[9] small and large artery endothelial dysfunction[10,11] and increased arterial stiffness.[12,13] Third, DM2 may cause a distinct metabolic cardiomyopathy related to hyperglycaemia and/or hyperinsulinaemia.[14-16]

The proximate causes of heart failure are left ventricular (LV) systolic and diastolic dysfunction. Previous studies on the association between glucose metabolism and LV function have not yielded consistent results, possibly because these studies were relatively small,[17-27] had targeted selected populations,[18,19,22-24,28] or dealt exclusively with DM2,[17-28] whilst population-based studies focused primarily on LV structure.[29-33] In addition, it is unclear whether LV dysfunction can also be detected in impaired glucose metabolism (IGM), i.e. impaired fasting glucose or impaired glucose tolerance.[29,34-36] The latter is of particular importance as investigations in IGM could give insight into the early development of DM2-related LV dysfunction.

In view of these considerations, we investigated, in a population-based cohort (n=746), the association between deteriorating glucose tolerance status on the one hand and echocardiographically determined LV systolic and diastolic function on the other. In addition, we explored the mechanisms underlying any such associations.

METHODS

Study population

For the present investigation we used data from the 2000 follow-up examination of the Hoorn Study[37] and data from the Hoorn Screening Study,[38] both of which were population-based. Details have been described elsewhere.[13] The entire study population consisted of 822 individuals (290 with a normal glucose metabolism (NGM), 187 with IGM, and 345 with DM2). Glucose tolerance status was determined by a single oral glucose tolerance test according to the 1999 WHO criteria (i.e. NGM: fasting glucose <7.0 mmol/l and post-load glucose <7.8 mmo/l; IGM: fasting glucose ≥7.0 mmol/l and postload glucose ≤11.1 mmol/l; DM2: fasting glucose ≥7.0 mmol/l and post-load glucose >11.1 mmol/l).

Echocardiography

A single ultrasound research technician blinded to the participants' clinical or glucose tolerance status obtained an LV echocardiogram according to a standardised protocol consisting of 2D, M-mode, spectral and colour flow Doppler recordings, with the use of an ultrasound scanner (HP SONOS 5500; 2-4 Mhz transducer, Andover, Massachusetts, USA). 2D recordings were performed in parasternal long- and short-axis views, and apical four- and two-chamber views.[39] Pulsed-Doppler spectral recordings were obtained with the sample volume placed at the tips of the mitral leaflets and, for the pulmonary venous flow, at the orifice of the right upper pulmonary vein. All recordings were digitally stored and analysed off-line according to international guidelines.[39]

We measured left atrial and ventricular diastolic and systolic diameters, and posterior wall (PWT) and interventricular septum thicknesses (IVS) from M-mode. Left atrial and ventricular systolic and diastolic volumes and ejection fraction were calculated from the apical four chamber view using the modified Simpson formula. Left ventricular mass was calculated as 0.8(1.04) $((EDD + IVS + PWT)^3 - EDD^3) + 0.6$ (in grams), and relative wall thickness as $(IVS + PWT)/EDD$. From the transmitral pulsed-Doppler recordings, we obtained peak E and A velocities, the ratio of early to late diastolic filling (E/A ratio) and the deceleration time E. Isovolumetric relaxation time was measured as the time from the end of aortic flow to the onset of mitral flow. From the pulmonary vein pulsed-Doppler recordings, we obtained the pulmonary vein flow A wave duration (A_{pv}) and the duration of the A wave (A_{mv}) over the mitral valve.[40] Each echocardiogram was inspected afterwards by a senior cardiologist blinded to the participants' clinical or glucose tolerance status to monitor quality of both recordings and readings.

Systolic and diastolic LV function

Normal LV systolic function was defined as ejection fraction ≥55%, and LV systolic dysfunction as ejection fraction <55%.[39] Normal LV diastolic function was defined as a sum score of 0 points, and LV diastolic dysfunction as a sum score ≥1 point, on the basis of the sum of three indices of late diastolic function, i.e., peak A velocity (0 points if <97 cm/s, 1 point if ≥97 cm/s); difference between A_{pv} and A_{mv} duration (0 points if <41 ms; 1 point if ≥41 ms); and left atrial volume (0 points if <57 ml, 1 point if ≥57 ml), where the cut-off values were 90th percentile in individuals with NGM. In addition, we analysed the E/A ratio on a continuous scale.

Other measurements

Health status, medical history, medication use and smoking habits were assessed by questionnaire.[37,38] We determined systolic and diastolic pressure, hypertension, glucose, glycated haemoglobin, insulin, serum total, high-density and low-density lipoprotein cholesterol, serum triglycerides, serum creatinine, (micro)albuminuria (as an estimate of (diabetic) microangiopathy), body mass index (BMI), waist-to-hip ratio and ankle-brachial pressure index as described elsewhere.[37,38] Insulin resistance was calculated according to the HOMA model.[41] Resting electrocardiograms were automatically coded according to the Minnesota Code.[15] Hypertension, prior cardiovascular disease and (micro) albuminuria were defined as described previously.[13,42] Endothelial function was estimated from noninvasive brachial flow-mediated vasodilation,[11,43] and central and peripheral artery stiffness from arterial ultrasonography, echocardiography and radial applanation tonometry.[12,13]

Statistical analyses

All analyses were carried out with SPSS (SPSS, Chicago, USA). We used analyses of covariance (ANCOVA), with linear contrast, to investigate trends in left atrial and ventricular mean values across categories of glucose tolerance. All statistically significant trends were tested on whether they deviated from linearity. The associations between glucose tolerance status and LV function were investigated with the use of logistic regression, in which LV dysfunction was classified as absent *vs* present (the 90th percentile definition). In addition, we analysed the E/A ratio on a continuous scale using linear regression analyses. In both these statistical methods glucose tolerance status was defined by dummy variables for IGM and DM2 with NGM as reference category. We first analysed the associations without any adjustments (crude model) and then with adjustments for potential confounders (adjusted models). As LV function is known to be affected by sex, age, hypertension and prior

Table 1. *Characteristics of the study population according to glucose tolerance status*

		Normal glucose metabolism	Impaired glucose metabolism	Type 2 diabetes mellitus	$P_{(trend)}$
No.	m/f	274 (133/141)	174 (86/88)	298 (160/138)	--
Age	years	68.5 ± 6.0	70.0 ± 6.2	66.9 ± 8.2	--
Systolic pressure	mmHg	137 ± 20	144 ± 16	148 ± 20	<0.001
Diastolic pressure	mmHg	75 ± 9	78 ± 9	79 ± 9	<0.001
Pulse pressure	mmHg	62 ± 16	67 ± 13	69 ± 15	<0.001
Mean pressure	mmHg	95 ± 11	100 ± 10	102 ± 11	<0.001
Hypertension	%	56	71	81	<0.001
Antihypertensive medication	%	25	35	51	<0.001
Total cholesterol	mmol/l	5.8 ± 1.0	5.8 ± 1.0	5.5 ± 1.1	0.003
HDL cholesterol	mmol/l	1.5 ± 0.4	1.4 ± 0.4	1.2 ± 0.3	<0.001
LDL cholesterol	mmol/l	3.7 ± 0.9	3.7 ± 0.9	3.5 ± 0.9	0.001
Triglycerides	mmol/l	1.2 (0.9-1.5)	1.3 (1.0-1.8)	1.6 (1.2-2.2)	<0.001
Lipid-lowering medication	%	13	17	20	0.03
Fasting glucose	mmol/l	5.4 ± 0.4	6.1 ± 0.5	7.7 ± 1.7	<0.001
Post-load glucose	mmol/l	5.6 ± 1.1	8.0 ± 1.6	11.7 ± 2.7	<0.001
Glycated haemoglobin	%	5.7 ± 0.4	5.9 ± 0.4	6.6 ± 0.9	<0.001
Fasting insulin*	pmol/l	46.0 (35.0-59.0)	65.5 (49.3-87.5)	83.5 (56.0-113)	<0.001
HOMA-IR*	AU	1.57 (1.16-2.04)	2.53 (1.87-3.19)	3.66 (2.54-5.47)	<0.001
Height	cm	169 ± 9	170 ± 9	169 ± 9	0.99
Weight	kg	75 ± 12	80 ± 13	83 ± 14	<0.001
Body mass index	kg/m²	26.1 ± 3.4	27.9 ± 4.0	28.9 ± 4.2	<0.001
Waist-to-hip ratio	--	0.90 ± 0.09	0.94 ± 0.08	0.96 ± 0.10	<0.001
Prior CVD	%	42	47	53	0.01
Serum creatinine	µmol/l	94.5 ± 14.1	94.8 ± 15.2	94.9 ± 19.5	0.80
(Micro) albuminuria	%	10	14	19	<.001
Smoking	%	15	18	13	0.38
SAC	ml/mmHg	1.1 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	<0.001
Carotid distensibility	10^{-3} kPa^{-1}	12.8 ± 4.2	11.6 ± 4.6	10.5 ± 4.3	<0.001
Brachial FMD#	mm	0.20 ± 0.15	0.19 ± 0.18	0.13 ± 0.17	<0.001

Data are reported as mean ± standard deviation or median (interquartile range). * n=733 as 13 individuals were on insulin therapy.
SAC = systemic arterial compliance (n=695); data on other measures of central and peripheral arterial stiffness have been reported elsewhere.[12,13]
FMD = flow-mediated vasodilation (n=543).[11]

cardiovascular disease (including coronary artery disease), these variables were considered first in the adjusted models. After we had assessed the main effects, interaction terms were used to investigate whether the association between glucose tolerance status and left ventricular function differed according to sex. Individuals with impaired fasting glucose (n=64) and impaired glucose tolerance (n=116) did not significantly differ from each other with regard to any of the analyses and were therefore combined.

Results are expressed as odds ratios with their 95% confidence interval. P values <0.05 were considered statistically significant.

RESULTS

Echocardiographic examinations

Of the 822 participants, 53 did not undergo the full standardised echocardiographic protocol for logistical reasons and in 23, a qualitatively satisfactory echocardiogram could not be obtained either due to a high body mass index (n=20; body mass index of subjects with an echocardiographic examination *vs* those without: 27.3 ± 3.8 kg/m^2 *vs* 36.4 ±7.9; p<0.001) or a poor transthoracic window (n=3). Further analyses were therefore based on 746 individuals (*table 1*).

Glucose tolerance and LV systolic function

Ejection fraction and fractional shortening decreased with deteriorating glucose tolerance status ($P_{(trend)}$ for both <0.001). LV end-systolic volume increased with deteriorating glucose tolerance status ($P_{(trend)}$ = 0.007). The prevalence of LV systolic dysfunction (standardised for age and sex) in NGM, IGM and DM2 was 13, 14 and 30%, respectively ($P_{(trend)}$ <0.001) (*table 2*).

Glucose tolerance and LV diastolic function

The prevalence in NGM, IGM and DM2 of peak A velocity ≥97 cm/s was 10% (by definition), 16 and 22%, respectively; of difference between A_{pv} and A_{mv} duration ≥41 ms, 10% (by definition), 11 and 14%; and of left atrial volume ≥57 ml, 10% (by definition), 14 and 24%. The prevalence of diastolic dysfunction (standardised for age and sex) in NGM, IGM and DM2 was 26, 36 and 47% ($P_{(trend)}$ <0.001). The E/A ratio decreased with deteriorating glucose tolerance ($P_{(trend)}$ = 0.007) (*table 2*).

Odds ratios for LV systolic and diastolic dysfunction

As compared with NGM, DM2 was significantly associated with LV systolic dysfunction (OR (95% CI), 2.44 (1.55 to 3.85)). The association remained statistically significant after additional adjustment for sex, age, hypertension, prior cardiovascular disease, body mass index and (micro)

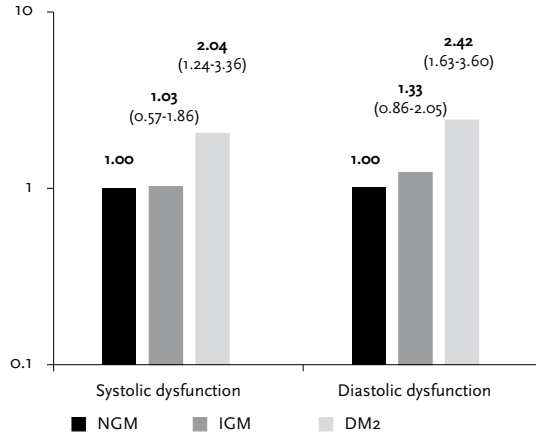
Table 2. *Left ventricular function according to glucose tolerance status*

	Normal glucose metabolism	Impaired glucose metabolism	Type 2 diabetes mellitus	$P_{(trend)}$
Prevalence of left ventricular dysfunction[a]				
Systolic dysfunction (%)	13	14	30	<0.001
Diastolic dysfunction (%)	26	36	47	<0.001
Estimates of systolic function				
Left ventricular end-systolic volume (ml)	38 (1)	38 (1)	42 (1.0)†	0.007
Ejection fraction	0.63 (0.01)	0.62 (0.01)	0.59 (0.01)†‡	<0.001
% of individuals with ejection fraction <55	13	14	30†‡	<0.001
Fractional shortening	46.9 (0.3)	46.5 (0.4)	44.7 (0.3)†‡	<0.001
Estimates of diastolic function				
Peak E velocity (cm/s)	64.7 (1.0)	65.0 (1.3)	69.1 (1.0)†‡	0.002
Peak A velocity (cm/s)	77.0 (1.0)	81.2 (1.3)#	87.2 (1.0)†‡	<0.001
% of individuals with peak A velocity ≥97	10	16#	22†‡	<0.001
E/A ratio	0.87 (0.01)	0.82 (0.02)	0.82 (0.01)†	0.007
Deceleration time E (ms)	244 (3)	237 (4)	241 (3)	0.53
Duration of A_{mv} (ms)	124 (1)	121 (1)	123 (1)	0.70
Duration of A_{pv} (ms)	139 (1)	136 (2)	144 (1)†‡	0.12
% of individuals with A_{pv}-A_{mv} ≥41	10	11	14†‡	0.20
Isovolumetric relaxation time (ms)	130 (3)	132 (4)	138 (3)	0.10
Left atrium volume (ml)	42 (1)	43 (1)	51 (1)†‡	<0.001
% of individuals with left atrium volume ≥57	10	14	24†‡	<0.001
Left ventricular end-diastolic volume (ml)	100 (1)	100 (2)	100 (1)	0.96

Data are reported as mean values (standard error) adjusted for age and sex, whereas the percentages of the individual measurements of left ventrical function were standardised for age and sex, with normal glucose metabolism as reference group. [a] For definitions see methods. †p<0.05 *vs* normal glucose metabolism. ‡p<0.05 *vs* impaired glucose metabolism. #p<0.05 *vs* =normal glucose metabolism.

albuminuria (OR, 2.04 (1.24 to 3.36)). IGM was not statistically significantly associated with LV systolic dysfunction (*table 3* and *figure 1*).
As compared with NGM, DM2 was significantly associated with LV diastolic dysfunction (OR, 2.54 (1.77 to 3.65)). The association remained statistically significant after additional adjustment for sex, age, hypertension, prior cardiovascular disease, body mass index and (micro) albuminuria (OR, 2.42 (1.63 to 3.60)). IGM was not statistically significantly associated with LV diastolic dysfunction after adjustment for hypertension and body mass index.
If we repeated the analyses with peak E, peak A and E/A ratio as continuous variables using regression analyses our results were not materially altered. However, the association between E/A ratio (i.e., a measure composed of both 'early' and 'late' diastolic dysfunction) and IGM reached statistical significance even after adjustment for prior cardiovascular disease and microalbuminuria (regression coefficient β (95% CI) -0.05 (-0.10 to -0.01) and -0.05 (-0.09 to -0.01) respectively (*table 4*; models 6 and 7).

Figure 1. *Adjusted odds ratios and their 95% confidence interval for left ventricular dysfunction across categories of glucose tolerance*



NGM = normal glucose metabolism; IGM = impaired glucose metabolism; DM2 = type 2 diabetes mellitus. NGM served as reference category. Adjustments were made for age, sex, hypertension, body mass index, prior cardiovascular disease, and (micro)albuminuria.

Results were similar when additionally adjusted for brachial flow-mediated vasodilation or measures of central and peripheral arterial stiffness (*table 3*, models 8 to 10).

To estimate the contribution of hyperglycaemia, hyperinsulinaemia and insulin resistance to the association between glucose tolerance status and left ventricular function, we compared the above analyses with those additionally adjusted for HbA1c (or fasting or postload glucose) and for insulin and insulin resistance. This showed that hyperglycaemia and hyperinsulinaemia explained 28% of the association of glucose tolerance with LV systolic dysfunction and 39% of that with LV diastolic dysfunction, with both variables contributing approximately equally (data not shown).

Additional analyses

The results of the logistic regression analyses for LV systolic dysfunction were not materially altered if the cut-off value for ejection fraction was set at 45% (data not shown).
The impact of a deteriorating glucose tolerance status on left ventricular function might be worse in women.[1] However, we found no interaction between DM2 and sex

Table 3. *Adjusted odds ratios for left ventricular dysfunction according to glucose tolerance status*

Model	Added variables	Systolic dysfunction		Diastolic dysfunction	
		Impaired glucose metabolism	Type 2 diabetes mellitus	Impaired glucose metabolism	Type 2 diabetes mellitus
1.	Crude	1.10 (0.62 to 1.95)	2.44 (1.55 to 3.85)	1.63 (1.07 to 2.46)	2.54 (1.77 to 3.65)
2.	Model 1 + sex	1.08 (0.61 to 1.93)	2.43 (1.53 to 3.88)	1.63 (1.07 to 2.46)	2.54 (1.77 to 3.65)
3.	Model 2 + age	1.10 (0.61 to 1.96)	2.38 (1.49 to 3.80)	1.50 (0.98 to 2.29)	2.98 (2.05 to 4.34)
4.	Model 3 + hypertension	1.06 (0.59 to 1.91)	2.22 (1.37 to 3.58)	1.41 (0.92 to 2.16)	2.63 (1.78 to 3.87)
5.	Model 4 + body mass index	1.06 (0.59 to 1.90)	2.13 (1.31 to 3.46)	1.33 (0.86 to 2.06)	2.46 (1.65 to 3.65)
6.	Model 5 + prior cardiovascular disease	1.04 (0.58 to 1.88)	2.08 (1.26 to 3.41)	1.33 (0.86 to 2.06)	2.44 (1.64 to 3.63)
7.	Model 5 + (micro-)albuminuria	1.03 (0.57 to 1.86)	2.04 (1.24 to 3.36)	1.33 (0.86 to 2.05)	2.42 (1.63 to 3.60)
8.	Model 5 + carotid distensibility*	0.98 (0.50 to 1.93)	2.02 (1.15 to 3.52)	1.38 (0.79 to 2.08)	2.20 (1.43 to 3.37)
9.	Model 5 + systemic compliance*	0.89 (0.45 to 1.77)	2.85 (1.67 to 4.84)	1.27 (0.77 to 2.10)	2.48 (1.59 to 3.87)
10.	Model 5 + flow mediated dilation*	1.08 (0.54 to 2.16)	3.26 (1.86 to 5.73)	1.31 (0.80 to 2.14)	2.32 (1.49 to 3.62)

Results are expressed as odds ratios (95% CI). Normal glucose metabolism serves as reference category. *For carotid distensibility: n=724; for systemic compliance: n=612; for flow-mediated dilatation: n=605.

Table 4. *Adjusted β-coefficients for conventional measures of left ventricular diastolic dysfunction*

Model	Added variables	Peak E velocity (cm/s)		Peak A velocity (cm/s)		E/A ratio (--)	
		Impaired glucose metabolism	Type 2 diabetes mellitus	Impaired glucose metabolism	Type 2 diabetes mellitus	Impaired glucose metabolism	Type 2 diabetes mellitus
1.	Crude	-0.05 (-3.31 to 3.21)	4.59 (1.76 to 7.41)	5.67 (2.08 to 9.25)	8.40 (5.29 to 11.52)	-0.07 (-0.12 to -0.03)	-0.03 (-0.08 to 0.01)
2.	Model 1 + sex	-0.00 (-3.21 to 3.20)	4.90 (2.12 to 7.68)	5.73 (2.26 to 9.21)	8.88 (5.86 to 11.90)	-0.07 (-0.12 to -0.03)	-0.04 (-0.08 to 0.01)
3.	Model 2 + age	0.31 (-2.89 to 3.51)	4.53 (1.76 to 7.30)	4.52 (1.22 to 7.82)	10.23 (7.36 to 13.10)	-0.06 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
4.	Model 3 + hypertension	-0.07 (-3.29 to 3.15)	4.78 (0.90 to 6.66)	3.90 (0.60 to 7.20)	8.99 (6.03 to 11.94)	-0.06 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
5.	Model 4 + body mass index	-0.80 (-4.04 to 2.43)	2.80 (-0.13 to 5.72)	3.26 (-0.75 to 6.59)	8.15 (5.13 to 11.17)	-0.05 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
6.	Model 5 + prior cardiovascular disease	-0.62 (-3.88 to 3.12)	2.12 (-0.89 to 5.13)	2.93 (-0.40 to 6.25)	7.30 (4.25 to 10.36)	-0.06 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
7.	Model 5 + (micro) albuminuria	-0.82 (-4.06 to 2.43)	2.75 (-0.20 to 5.71)	3.19 (-0.14 to 6.51)	7.89 (4.86 to 10.92)	-0.05 (-0.10 to -0.01)	-0.05 (-0.09 to -0.00)

Results are expressed as β-coefficients (95% CI). Normal glucose metabolism serves as reference category.

(all p values ≥0.13), which means that within our data no significant sex differences existed in the relationship between left ventricular function and glucose tolerance status. Results were not materially altered if we replaced hypertension by any of the other blood pressure variables, or if we replaced body mass index by body surface area or waist-to-hip ratio (data not shown).

The results of the logistic regression analyses for LV diastolic dysfunction were not materially altered if we excluded those with an ejection fraction <45% (n=23) (data not shown).

Results were also similar when additionally adjusted for lipid profile, use of lipid-lowering or antihypertensive medication (including ACE inhibitors), smoking, serum creatinine and LV wall motion abnormalities (data not shown).

If we replaced the P90 cut-off values for LA volume and A_{pv}-A_{mv} wave duration for published cut-off values[44,45] or chose the P95 as cut-off value, our results were not materially altered.

DISCUSSION

This study had four main results. First, as compared with NGM, DM2 was associated with a 2.0-fold greater risk of LV systolic dysfunction and a 2.4-fold greater risk of LV diastolic dysfunction. Second, these higher risks could not be explained by higher blood pressure or greater obesity, which are often observed in DM2, nor by DM2-associated impairment of large and small artery function, as estimated from the prevalence of prior cardiovascular disease and (micro)albuminuria, and from large artery endothelium-dependent vasodilation and stiffness. Third, a considerable part of LV dysfunction in DM2 (about 30 to 40%) was explained by hyperglycaemia and hyperinsulinaemia. Fourth, in this elderly population, IGM was not significantly associated with impaired LV function using the definition based upon the 90th percentile of diastolic dysfunction (DDF) parameters, but was associated with DDF using linear regression analyses with the E/A ratio on a continuous scale. These findings may thus explain why DM2 increases the risk of systolic and diastolic heart failure, and additionally argue in favour of a distinct metabolic cardiomyopathy in elderly individuals with DM2. In elderly individuals with IGM this is less clear.

Our study was comprehensive and had important advantages over previous studies on the association between glucose tolerance and LV function, which were relatively small,[17-27] targeted selected populations,[18,19,22-24,28] or dealt exclusively with DM2[17-28] whilst population-based studies focused primarily on LV structure in relation to LV systolic dysfunction.[29-33]

Our results on systolic dysfunction are in concordance with a study by Celentano *et al.*,[17] who studied 64 telephone company employees, the HyperGen Study[30] and two Strong Heart Study reports.[29,31] However, the Cardiovascular Health Study (CHS),[32] somewhat unexpectedly, did not observe systolic dysfunction in DM2.

Our study is the first to observe a clear association between DM2 and LV diastolic dysfunction in a large (Caucasian) general population-based study, designed to investigate the differences between NGM, IGM and DM2. Previous studies[18,19,22,25,29,32,36] may have failed to detect a consistent association of DM2 with LV diastolic dysfunction because of the use of echocardiographic measures of both *early* and *late* LV diastolic filling (i.e., the E/A ratio) which can be

hampered by the phenomenon of 'pseudo-normalisation' (i.e., an apparently normal LV diastolic filling pattern due to increased LA pressure, as a direct consequence of decreased LV compliance).[46] Interestingly, in our study a significant relationship did exist between the E/A ratio and glucose tolerance status. The reason for this discrepancy is not clear. However, to further overcome the phenomenon of pseudo-normalisation, we also analysed measurements of *late* diastolic performance (i.e., peak A velocity, A_{pv}-A_{mv} duration and LA volume) and combined these into a simple sum score, which has the advantage of excluding active myocardial relaxation during diastole[46] and thus providing optimal characterisation of passive stiffness of the LV chamber.

The mechanisms linking DM2 to systolic and diastolic LV dysfunction are incompletely understood. We found no evidence that DM2-associated hypertension and obesity played a role. In addition, our data do not support an important role for DM2-induced impairment of large and small artery function. However, the validity of this conclusion depends on the accuracy of the estimates of arterial function we used. For example, we used brachial artery endothelium-dependent vasodilation and (micro) albuminuria as estimates of coronary epicardial and microvascular function, respectively, and this may be insufficiently precise. Therefore, future studies to address these issues should use more sophisticated techniques.

Interestingly, indices of hyperglycaemia and hyperinsulinaemia (or insulin resistance) explained about 30 to 40% of the association between DM2 and LV dysfunction, supporting the existence, in these elderly individuals, of a distinct metabolic cardiomyopathy.[14,47,48] Hyperglycaemia and hyperinsulinaemia may impair LV function through several pathways, the relative importance of which is not completely understood. First, hyperglycaemia alters intracellular calcium homeostasis, leading to depressed contractile function.[49,50] Second, hyperglycaemia increases oxidative and carbonyl stress,[51] which may lead to a chronic, low-grade inflammatory response and cross-linking of myocardial proteins, which may promote myocardial fibrosis and impair LV compliance, effects that may be enhanced by the growth promoting properties of hyperinsulinaemia.[52,53]

It is not known whether IGM is independently associated with risk of heart failure. In our study, IGM was not associated with systolic dysfunction, and the association with diastolic dysfunction (based upon the 90th percentile definition) was explained by body mass index and hypertension. However, the association between IGM and DDF estimated from the E/A ratio remained after multivariate adjustment. Therefore, we conclude that IGM was associated with DDF but not with SDF.

Our study had several limitations. First, we cannot exclude that our results have been influenced by the co-existence of (subclinical) cardiovascular disease affecting both LV wall motion and shape. To address this concern, we adjusted for prior cardiovascular disease in our statistical analyses. Moreover, our results were not materially altered when additionally adjusted for wall motion abnormalities (data not shown). Second, our results were obtained in elderly individuals. Therefore, we may have underestimated the association of LV dysfunction with glucose tolerance due to a healthy survivor effect. Finally, as our study was cross-sectional in nature, causality should be inferred with caution and it remains to be determined whether our results can be generalised to other ethnicities.

We conclude that DM2 is independently associated with a 2.0 greater risk of LV systolic dysfunction and a 2.4 greater risk of LV diastolic dysfunction. This may explain the increased risk of systolic and diastolic heart failure in elderly individuals with DM2.

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